NOVEL COMPOUNDS TO TREAT DIABETES AND ASSOCIATED CONDITIONS

BACKGROUND OF THE INVENTION

The present application is directed to novel antidiabetic compounds.

The causes of Type I and Type II diabetes are still unknown, although both genetic and environmental factors seem to be involved. Type I diabetes (or insulin-dependent diabetes) is an autonomic immune disease in which the responsible autoantigen is still unknown. Patients with Type I diabetes need to take insulin intravenously to survive. Type II diabetes (formerly referred to as non-insulin dependent diabetes) is a metabolic disorder resulting from the body's inability either to make a sufficient amount of insulin or to properly use the insulin that is produced. Insulin secretion and insulin resistance are considered the major metabolic defects, but the precise genetic factors involved remain unknown.

Patients with diabetes usually have one or more of the following defects:

- Under-production of insulin by the pancreas
- Over-secretion of glucose by the liver
- Defects in glucose transporters
- Desensitization of insulin receptors
- Defects in metabolic breakdown of polysaccharides

In addition to the IV administration of insulin, currently available medications used for diabetes include 4 classes of oral hypoglycemic agents listed in the following table.

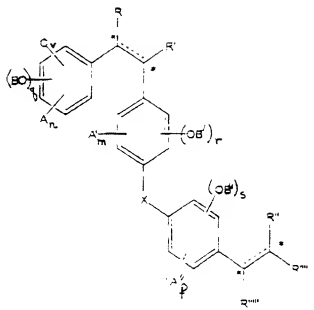
Class	Marketed Drugs	Mechanism of Action	Limitations
Sulfonylureas	First generation: 2 Second generation: 3	Signals beta cells to release more insulin	Development of resistance Hypoglycemia
Biguanides	Metformin	Reduces hepatic glucose production Improves	Adverse hepatic effects Lactic acidosis Unwanted

		Improves sensitivity to insulin	Unwanted gastrointestinal effects
Glucosidase inhibitors	Acarbose	Reduces glucose absorption from gut	Works only after meals GI side effects
Thiazolidinediones	Troglitazone Rosiglitazone Piaglitazone	Reduce insulin resistance	Not effective in 25% of patients Require frequent liver function tests Have very long onset of action Cause weight gain

As is apparent from the above table, there are disadvantages to each of the currently available agents for use in the treatment of diabetes. Accordingly, there is a continuing interest in the identification and development of new agents, particularly orally administered, water-soluble agents that can be used for the treatment of diabetes.

SUMMARY OF THE INVENTION

Compounds having the general formula (I)-(III) have glucose-lowering activity.



(I)

Stereocenters (designated by *) could be R- or S-.

Each bond represented by dotted lines could be a double or a single bond, and the geometry across the bond could be E or Z.

R and R' are independently H or C_1-C_{20} linear or branched alkyl or alkenyl groups that may be substituted, or functional groups like $COOR_3$, where R_3 = H, a cation C_1-C_{20} linear or branched alkyl or C_5-C_{10} aryl; $CONR_1R_2$, where R_1 and R_2 may be independently or together H, linear or branched C_1-C_{20} alkyl or C_5-C_{20} aryl, NH_2, OH, C_1-C_{20} linear or branched alkoxy, halo, cyano, or R+R'=O.

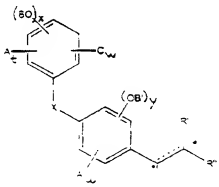
A, A', A'', and C are independently H, C_1-C_{20} acylamino, C_1-C_{20} acyloxy, linear or branched C_1-C_{20} alkanoyl, C_1-C_{20} alkoxycarbonyl, C_1-C_{20} linear or branched alkoxy; C_1-C_{20} linear or branched alkylamino, C_1-C_{20} alkylcarboxylamino, C1-C_{20} carbalkoxy; carboxyl, cyano, halo, hydroxy; and n, m, and p are independently integers from 0 to 3;

B, B', and B" are independently H, C_1-C_{20} acylamino, C_1-C_{20} acyloxy; C_1-C_{20} linear or branched alkanoyl, C_1-C_{20} linear or branched alkenyl, C_1-C_{20} alkoxycarbonyl, C_1-C_{20} linear or branched alkoxy; C_1-C_{20} linear or branched alkyl amino, C_1-C_{20} alkyl carboxyl

amino, C_1-C_{20} carbalkoxy; aroyl, araalkanoyl, carboxyl, cyano, halo, hydroxy; and q, r and s are independently integers from 0 to 3;

R''', R'''' and R''''' are independently H, C_1-C_{20} linear or branched alkyl or alkenyl groups which may contain substituents, COOH, C_1-C_{20} alkoxycarbonyl, NH_2, $CONH_2$, C_1-C_{20} acylamino, C_1-C_{20} alkoxycarbonyl, OH, C_1-C_{20} alkoxy, halo, or cyano.

X = NH, O, S, S=O, or SO_2.



(II)

Stereocenters (designated by *) could be R- or S-.

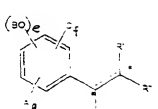
Each bond represented by the dotted line could be a double or a single bond, and the geometry across it may be E or Z.

A, A', and C are independently H, C_1-C_{20} acylamino, C_1-C_{20} acyloxy, C_1-C_{20} alkoxycarbonyl, C_1-C_{20} alkoxy, C_1-C_{20} linear or branched alkyl amino, C_1-C_{20} alkylcarboxylamino, C_1-C_{20} carbalkoxy; carboxyl, cyano, halo, hydroxy; and t, u, and w are independently integers from 0 to 3;

B and B' are independently H, C_1-C_{20} acylamino, C_1-C_{20} acyloxy; C_1-C_{20} alkanoyl, C_1-C_{20} alkenoyl, C_1-C_{20} alkenyl, C_1-C_{20} alkoxycarbonyl, C_1-C_{20} linear or branched alkoxy, C_1-C_{20} linear or branched alkyl amino, C_1-C_{20} alkylcarboxylamino, C_1-C_{20} carbalkoxy, C_6-C_{20} aroyl, C_6-C_{20} araalkanoyl, carboxyl, cyan, halo, hydroxy; and x and y are independently integers from 0 to 3;

R', R'', and R''' are independently H or C_1-C_{20} linear or branched alkyl or alkenyl groups which may contain substituents, COOH, C_1-C_{20} alkoxycarbonyl, NH_2, $CONH_2$, C_1-C_{20} acylamino, C_1-C_{20} alkoxycarbonyl, OH, C_1-C_{20} alkoxy, halo or cyano.

X = NH, O, S, S=O, or SO_2



(III)

Stereocenters (designated by *) could be R- or S-.

The bond represented by the dotted line could be a double or a single bond, and the geometry across it may be E or Z.

A and C are independently H, C_1-C_{20} acylamino, C_1-C_{20} acyloxy, C_1-C_{20} linear or branched alkanoyl, C_1-C_{20} alkoxycarbonyl, C_1-C_{20} linear or branched alkoxy, C_1-C_{20} linear or branched alkyl amino, C_1-C_{20} alkylcarboxylamino, C_1-C_{20} carbalkoxy; carboxyl, cyano, halo, hydroxy; thiol, SOR or SOR_2; and f and g are independently integers from 0 to 3;

B is independently H, C_1-C_{20} acylamino, C_1-C_{20} acyloxy; C_1-C_{20} linear or branched alkanoyl, C_1-C_{20} linear or branched alkenoyl, C_1-C_{20} linear or branched alkenyl, C_1-C_{20} alkoxycarbonyl, C_1-C_{20} linear or branched alkoxy, C_1-C_{20} linear or branched alkyl amino, C_1-C_{20} alkylcarboxylamino, C_1-C_{20} carbalkoxy, C_5-C_{20} aroyl, C_6-C_{20} araalkanoyl, carboxyl, cyan, halo, hydroxy; and e is an integer from 1 to 3;

R', R'', and R''' are independently H or C_1-C_{20} linear and branched alkyl or alkenyl groups which may contain substituents, COOH, C_1-C_{20} alkoxycarbonyl, NH_2, $CONH_2$, C_1-C_{20} acylamino, C_1-C_{20} alkoxycarbonyl, OH, C_1-C_{20} alkoxy, halo, cyano.

Brief Description of the Drawings

Figure 1 shows the blood glucose concentrations found in ob/ob mice given the representative compound at a dose of 50 mg/kg for 7 days.

Figure 2 shows the blood glucose concentrations found in diabetic ob/ob mice given the representative compound at doses of 0 (vehicle), 10, 25, or 50 mg/kg for 7 days (left); and those found in lean ob/ob mice given the representative compound at a dose of 50 mg/kg for the same period (right).

Figure 3 shows the serum triglyceride concentrations and systolic blood pressure of fructose-fed, insulin-resistant rats that received the representative compound or the vehicle for 7 days.

Figure 4 shows the glucose uptake of 3T3-L1 cells exposed to two different concentrations of the representative compound (0.1 nM and 0.1 μM).

Figure 5 shows the levels of PPAR-γ expression found in adipose tissue of ob/ob mice treated with the vehicle or the representative compound (50 mg/kg) for 10 days.

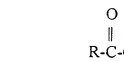
DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the compounds of the formulas I, II and III, the alkyl groups may be linear or branched including but not limited methyl, ethyl, propyl, isopropyl, sec-butyl, n-butyl, pentyl, isopentyl, and the like. Alkenyl groups of 1 to 20 carbon atoms includes but is not limited to, ethylene, propylene, butylene, isobutylene, and the like. Aryl groups include phenyl, and other multi-ring aromatic structures. Alkoxy includes methoxy, ethoxy propoxy, isopropoxy, n-butoxy, isobutoxy and the like. Halo includes bromo chloro, fluoro, iodo.

Acylamino includes the group

wherein R could be hydrogen alkyl or aryl.

Acyloxy includes the group



wherein R is hydrogen, alkyl or aryl.

Alkanoyl includes the group

wherein R can be hydrogen, alkyl or aryl.

Alkoxy carbonyl includes the group

wherein R can be alkyl.

Alkylamino includes the group

wherein the amino group may be mono or di-substituted with alkyl groups.

Alkylcarboxylamino includes the group

wherein R can be an alkyl group.

Carboalkoxy includes the group

wherein R is an alkyl group.

Aroyl includes the group

wherein R is aryl.

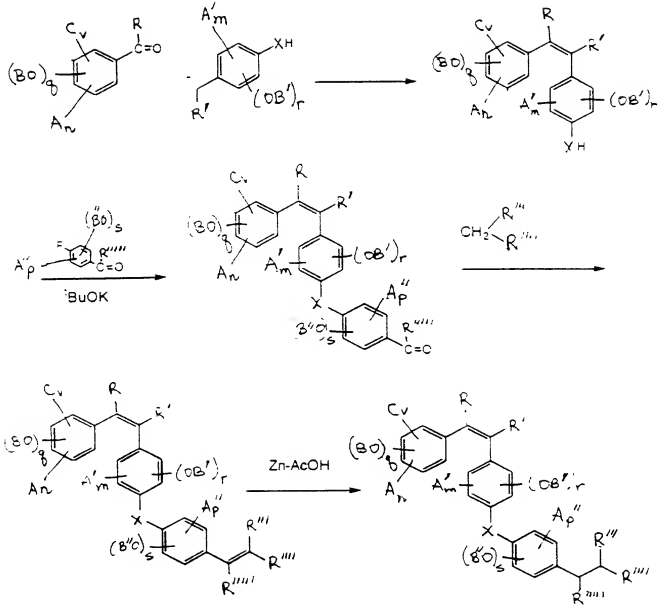
Araalkanoyl includes the group

wherein R is aryl and R^1 is alkylenyl.

Preferred compounds of formula are those wherein C and A are hydrogen, and q=2 when B is methyl. Other preferred compounds are those in which A' is hydrogen and r=O, and in which A" is hydrogen and s=O. Another preferred class of compounds comprises those in which R is hydrogen and R' is $-COOR_3$. A preferred class of substituent comprises those in which R"" is hydrogen. R''' and R"" are independently $-COOR_3$ and X is oxygen.

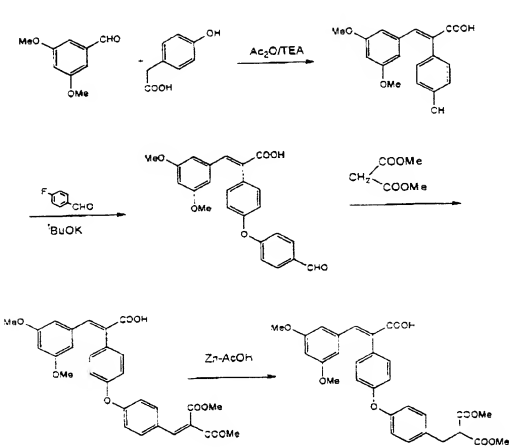
The method used for the synthesis of the representative member of the Type (I) compounds is shown in Scheme I.

Scheme I



A specific method for the synthesis of a representative number of compounds of the formula I is show below in Scheme IA. Compounds of the formula II where made starting from the second step showing in Scheme I with the appropriate starting materials. The compounds of formula III may be made by utilizing the chemistry of the last step of Scheme I using the appropriate starting materials.

Scheme IA



The compounds of the present invention are useful in the treatment of diseases or disorders characterized by the presence of the elevated blood glucose levels, that is hyperglycemic disorders, such as diabetes melitis, including both type I and II diabetes as well as other hyperglycemic related disorders such as obesity, increased cholesterol kidney related disorders, and the like. The compounds are preferably administered at least to reduce the blood glucose level in the host suffering from the hyperglycemic disorder. The sufficient amount of the compound is administered to the subject to reduced the blood glucose level to an acceptable range which is typically about plus or minus 10%, usually plus or minus 8%, and more usually plus or minus 5% of the normal average blood glucose level for the subject. A variety hosts may be treated with the compounds to reduce blood glucose levels, such as humans and including mammalians host such a livestock, valuable or rare animals, pets, such as dogs and cats. The compounds may be administered by any convenient administration technique including, but not limited to, intravenous, intradermal, intramuscular, subcutaneous, or oral. The dosage delivered to the host will necessarily depend upon the route by which the compound is administered but will generally range from about 50-500mg/70kg human body weight, and usually from about 100-200mg/70kg human body weight.

The compounds will be combined in a physiologically acceptable vehicle to produce a pharmaceutical composition. The nature of the physiologically acceptable vehicle will necessarily depend on the method for which the pharmaceutically composition is administered. Exemplary vehicles include water, that is, sterile water for injection, saline, such as phosphate buffered saline, lyophilized power in the form of tablets or capsules where such forms may include various fillers binders and the like. The amount of the active compound in the pharmaceutical composition will be selected in view of the method by which the pharmaceutical composition is to be administered, and may be determined empirically by those of ordinary skill in the art.

Figures 1 through 5 present the results of preclinical tests performed using a compound according to the present invention, 4-(1-carboxy-2-(3,5-dimethoxyphenyl)) ethylenyl-4'-(2,2-dicarbomethoxy) ethyl diphenyl ether.

When 6-week-old male ob/ob mice were given a 50 mg/kg dose of this compound or the vehicle daily for 7 days, the blood glucose concentrations of the mice given the

compound were reduced 50% from those of the mice given the vehicle only, and the reductions of blood glucose concentrations were observed as early as Day 2 (see Figure 1).

In another experiment, 6-week-old male diabetic ob/ob mice received the indicated oral doses of the test compound daily. Figure 2 shows that the 10mg/kg dose of the compound lowered blood glucose concentrations as effectively as the 50mg/kg dose. The blood glucose concentrations in lean control animals given the highest dose of the test compound (50 mg/kg) did not differ from those in animals given vehicle only.

The ability of this test compound to lower serum triglyceride concentrations and blood pressure was studied in fructose-fed, insulin-resistant rats. For this experiment, male Sprague-Dawley rats initially weighing 150-175g were placed on a 60% fructose-enriched diet for 10 days. On Day 11, rats with hypertriglyceridemia were randomly assigned to receive oral doses of vehicle or the compound (50mg/kg) daily for 7 consecutive days. Serum triglyceride concentrations were measured 24 hours after each administration of test agent, and blood pressure was measured 18 hours after test agent administration. Figure 3A shows that the test compound effectively lowered serum triglyceride concentrations in these rats, and Figure 3B shows that the rats treated with the test compound had significantly lower blood pressure than did those treated with vehicle.

Basal glucose uptake of 3T3-L1 cells was measured in the presence of two different concentrations of the test compound (0.1 nM and 0.1 μM). Cells were incubated at 37°C for 48 hours with vehicle or the test compound, and then further incubated with ^{14}C-deoxyglucose for an additional 30 min at 22°C. The cells were washed and lysed, and the total radioactivity in the cells was measured. Figure 4 shows that the glucose uptake increased over the basal level in cells treated with the test compound. This result suggests that this test compound stimulates glucose uptake in differentiated adipocytes.

In an experiment studying the expression of PPAR-γ in the adipose tissue of mice, epididymal fat was collected from six different ob/ob mice either treated with vehicle or the test compound (50 mg/kg) for 10 days, homogenized in lyses buffer, and centrifuged. A total of 30 mg of protein was loaded on to SDS polyacrylamide gel, immunoblotted, and probed with anti PPAR-g antibody raised against a 15-residue synthetic peptide containing conserved sequences of PPAR-g (see Figure 5A). The bands were quantified and represented in bar graphs (see Figure 5B). The expression levels of PPAR-g in the tissues from vehicle-treated and the compound-treated animals did not differ from each other.

The tests described above and illustrated in the figures show that the compounds according to the present invention lower blood glucose concentrations, lower serum triglyceride concentrations, lower systolic blood pressure, and increase glucose uptake by adipose tissue, but do not affect the expression of PPAR-γ by adipose tissue.